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(54) Pharmaceutical compositions comprising cyclosporin as active ingredient

(57) The invention disclosed a homogenous substantially alcohol free composition of Cyclosporin which comprises a Cyclosporin in a hydrophilic carrier medium comprising propylene glycol, esters of propylene glycol with C4 to C12 fatty acids and polyoxyethylene hydrogenated castor oils wherein the ingredients are present in the following ranges, Cyclosporin 1 - 25% w/w, Propylene Glycol 2.5 - 70% w/w. Esters of Propylene Glycol with C4 to C12 fatty acids 2.5 - 70% w/w and Polyoxyethylene hydrogenated Castor oils 2.5 - 70% w/w.

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Description

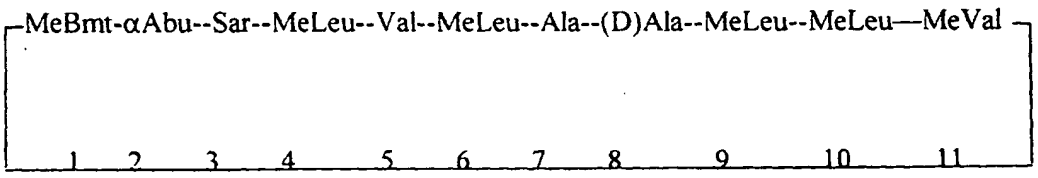
INTRODUCTION

[0001] The present invention relates to pharmaceutical compositions comprising Cyclosporin as active ingredient. The present invention also relates to novel alcohol free, free flowing, clear and transparent compositions comprising Cyclosporin as an active ingredient. The novel compositions are characterised in having increased bio-availability when the drug is formulated in a solubilised system and also amenable to convenient commercial production.

BACKGROUND OF THE INVENTION

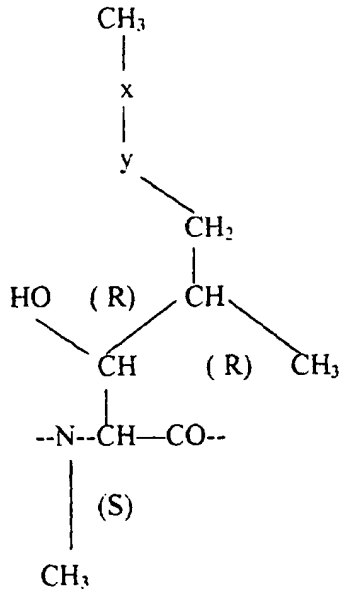
[0002] Cyclosporins comprise a class of structurally distinctive, cyclic, poly-N-methylated endecapeptides, commonly possessing pharmacological, in particular immunosuppressive, anti-inflammatory and/or anti-parasitic activity. The first of the Cyclosporins to be isolated was the naturally occurring fungal metabolite Ciclosporin or Cyclosporine, also known as Cyclosporin A and commercially available under several brands. Ciclosporin is the Cyclosporin of formula A.

(A)



wherein - MeBmt- represents the N-Methyl-(4R)-4-but-2E-en-1-yl-4-methyl-(L) threonyl residue of formula B.

(B)



in which -x-y- is --CH =CH-- (trans).

[0003] Naturally occurring and semi-synthetic Cyclosporins, their classification, nomenclature etc. are known [c.f Traber et al. 1, Helv. Chim Acta. 60, 1247-1255 (1977): Traber et al. 2, Helv. Chim. Acta. (65 no. 162, 1655-1667 (1982)); Kobel et al., Europ. J. Applied Microbiology and Biotechnology 14, 273-240(1980): and von Wart -burg et al., Progress in allergy , 38,28-45(1986)]. US Patent Nos 4,108,985, 4,210,581 and 4,220,641; European Patent Publication Nos. 0034567 and 0056782: International Patent Publication no. WO 86/02080; Wenger 1, Transp. Proc. 15, Suppl.

1; 2230(1983); Wenger 2, Angew. Chem. Int. Ed., 24,77 (1985); and Wenger 3, Progress in Chemistry of Organic natural Products 50, 123(1986). Other Cyclosporins are known from U.S Patents 4,639,434; 4,703,033; 4,764,503, 4,885,276; 5,116,816; 5,122,511; 5,525,590; 5,643,870 and 5,767,069.

[0004] So far the primary area of clinical investigation for cyclosporins and in particular, Ciclosporin has been as an immunosuppressive agent, in particular in relation to its application to recipients of organ transplants, e.g. heart, lung, combined heart-lung, liver, kidney, pancreatic, bone-marrow, skin and corneal transplants and, in particular, allogenic organ transplants. In this field Cyclosporins, in particular ciclosporins have achieved a remarkable success. Among all the Cyclosporins. Cyclosporin A (also known as Cyclosporine or Ciclosporin) has established its utility in the area of organ transplant and therapy of autoimmune diseases.

[0005] At the same time, applicability of Cyclosporins including Ciclosporin to various autoimmune diseases and to inflammatory conditions, in particular inflammatory conditions with an aetiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases, has been intensive and reports and results in vitro, in animal models and in clinical trials are wide-spread in the literature. Specific auto-immune diseases for which Cyclosporin and Ciclosporin therapy has been proposed or applied include, autoimmune hematological disorder (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopaenia), systemic lupus erythematosus, poly-chondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis and Crohn's disease) endocrine opthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthirits and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy).

[0006] Further areas of investigation for cyclosporins include potential applicability as an anti-parasitic, in particular anti-protozoal agent, with possible uses suggested including treatment of malaria, coccidiomycosis and schistosomiasis and, yet more recently, use as an agent for reversing or abrogating anti-neoplastic agent resistance in tumours and the like.

[0007] Although Cyclosporin A is the most widely used amongst all the immunosuppresants available so far, it suffers from a serious drawback of poor bio-availability. Cyclosporin blood levels have to be maintained within a specified range to achieve the effective therapy. The required range varies according to the clinical status of the patient.

[0008] Because of poor and variable bioavailability daily dosages needed to achieve the desired blood levels need to be varied considerably in the existing dosage forms of Cyclosporin and a concomitant monitoring of blood levels is essential. This adds an additional cost to the therapy.

[0009] In order to improve the bio-availibility several attempts have been made to improve formulations of Cyclosporin.

Han Gua Patent (Chinese Patent No. 94191895.5) explains the active compound of Cyclosporin, fatty acid sugar ester and diluent carrier having good bio-availability. However, this compound suffers from the drawback that diluent degrades due to hygroscopicity of sugar ester and the stability is not of desired standards, (See also Pharmaceutical Research, Volume 6, No. 11, 1989, P958, "Solid Surfactant Solution of active Ingredients in Sugar Ester" and International Journal of Pharmaceutics, Vol. 92, 1993, P197," Application of sucrose laurate a new pharmaceutical excipient, in Peroral formulation of Cyclosporin A").

[0010] Chinese Patent 9419189.5 having equivalent EP 0702562 describes a powder dosage form of Cycloproin possessing comparatively higher stability and to some extent bio-availability when compared to the earlier formulations. This art describes adsorption of Cyclosporin A with appropriate solvents onto an adsorbent along with a nonionic hydrophillic surfactant. The final product does not contain the solvent as this evaporates during the process of manufacturing. Thus this product does not suffer from the disadvantage arising out of solvent evaporation during shelf life and hence stability problems. The various pharmaceutical surfactants, polyhydric alcohols and solvents are well known to the art. The adsorbent used is Colloidal Silicon Dioxide. The blood level arising out of such product have been compared with the standard formulations as per US patent no. 4, 388, 307 with significant improvement in bioavailability. However, when compared with the micro-emulsion based formulations (described later) these formulations do not show any advantage as the drug is adsorbed on solid surface and needs an additional process of dissolution prior to become bioavailable.

[0011] The effect of sucrose laurate on the gastrointestinal absorption of Cyclosporine is also described (Lerk-PC; Sucker-H, International Journal of Pharmaceutics; 1993; 92; (May 3); 197-202). The evaluation of the dosage form containing sucrose Laurate was found to enhance the in vitro absorption of Cyclosporine when normal epithelial tissue and Peyer's patch tissue of guinea pigs were used. Compared to the commercially available drinking solution, absorption was raised by a factor of 10. Excess amount of surfactant reduced drug absorption. Despite large excess of Sucrose laurate, the absorption of Cyclosporin was still superior to the drinking solution. Choleic acid was also found to increase absorption by a factor of 5-6. A comparison of the absorption between normal epithelial and Peyer's patch tissues

indicated that the absorption by endocytosis does not contribute significantly to the overall absorption of Cyclosporin. It was concluded that preliminary formulation experiments showed that a solid oral dosage form of Cyclosporin could be made using sucrose laurate as an excipient.

[0012] Abdallah-HY; Mayersohn-M. Pharmaceutical Research; 1991;8(Apr);518-522 reported several formulations of Cyclosporin were prepared and examined in vitro and in dogs.A tablet formulation was then selected for comparison with the commercial oil solution placed in a soft gelatin capsule in a randomized crossover study in dogs. Compared with an intravenous dose of the drug, absolute bioavailability was 46+11.1 and 45+ 9.9% for the capsules and tablets, respectively. Maximum concentration, time to reach maximum concentration and mean absorption time were not significantly different between the 2 formulations. It was concluded that the tablet formulation of Cyclosporin is equivalent in dogs to the commercial dosage form packed into soft gelatin capsules.

[0013] US patent no. 505 1402 describes that Cyclosporin may be rendered more soluble by the concomitant administration of α-Cyclodextrin, either separately, but essentially simultaneously or, preferably, in admixture.

[0014] US Patent No. 4990337 describes a formulation comprising a Cyclosporin in admixture with at least one mono or diglyceride of a C_6- C_{10} fatty acid sufficient to dissolve the Cyclosporin. The resulting solution can then easily be emulsified in water or an aqueous fluid.

[0015] Freeze dried liposome mixture containing Cyclosporin has been described in US Patent no. 4963362. This invention provides a freeze-dried potential liposome mixture having an amphipathic lipid and a Cyclosporin or derivative thereof for use in possible liposome delivery of Cyclosporin into cells. A method to produce the freeze-dried mixture is also disclosed. When reconstituted to yield liposomes in an aqueous medium, substantially all of the Cyclosporin present in the freeze-dried mixture is encapsulated in the liposomes.

[0016] Other galenic improvements in Cyclosporin emulsion formulations recorded in prior art are the use of tocopherol derivatives (EP 0724452), tocopheryl polyethylene glycol carboxylic acid ester (EP 0712631), dimethylisosorbide (EP 0711550, EP 0650721), alkylene polyether or polyester (WO 9423733), emulsion compositions (EP 0694308), anhydromannitol oleylether, lactoglyceride, citroglycerides (EP 656212), phosphatidyl ethanolamine (EP 0651995), as surfactants and stabilizers etc.

[0017] Three Patent Applications namely European Patent App. No. 94110184.2, 95117171.9 and PCT/EP95/04187 describe the use of Dimethylisosorbide as a co-surfactant or a hydrophillic phase along with other ingredients to enhance the absorption of Cyclosporin.

[0018] Thomas Cavanak in U.S. Pat. no. 4,388,307 have described compositions employing ethanol, olive oil as carrier medium in conjunction with Labrafil as surfactant. These compositions yield crude emulsions on dilution with water. The bio-availability levels using these dosage forms are low and exhibit wide inter-and intra-individual variations. Such dosage forms provide an average absolute bioavailability of ca 30%. Reported variation in bio-availability between subjects varies between a few percent for some patients to as much as 90% or more for others. Also a marked change in bio-availability for individuals with time is frequently observed.

[0019] U.S. Patent no. 5,977,066 discloses oral compositions using monoglycerides, diglycerides and triglycerides alongwith castor oil derivatives. Compositions of the present invention do not contain fatty materials like mono-,di-, or triglycerides.

U.S. Patent no. 6,022,852 discloses the use of tocopherol polyethylene glycol 1000 succinate for formulating Cyclosporin A.

[0020] Hong et al. In U.S. Patent no. 6,028,067 disclose the use of lipophilic solvent chosen from an alkyl ester of polycarboxylic acid and a carboxylic acid ester of polyols, alongwith an oil; and a surfactant to form microemulsion preconcentrate of cyclosporin A. Such lipophilic solvents are not present in the present invention.

[0021] Sherman Bernard Charles (WO9848779) claim an emulsion preconcentrate comprising a cyclosporin dissolved in a solvent system comprising acetylated monoglycerides, and a surfactant.

Robert Floc'h et al. In U.S. Patent no. 5, 827, 822 disclosed aqueous suspension of amorphous Cyclosporin nanoparticles wherein at least 50 percent of the drug is present as particles of less than about I μm.

[0022] One of the most significant attempt to improve bio-availability of Cyclosporin from its dosage form is the described in US patent no. 5, 342, 625. This art describes use of microemulsion pre-concentrate consisting of a three phase systems i.e. (1) a hydrophilic phase component (2) a lipophilic phase component and (3) a surfactant. Such composition has alcohol as an essential ingredient. Such composition upon dilution with water provides an oil-in-water microemulsion with an average particle size of less than 1000A°. Such an enhanced surface area results in increased bio-availability of Cyclosporin when compared with conventional dosage forms. A comparison of bio-availability from micro-emulsion dosage form (Composition I from US patent no. 5, 342, 625) with the conventional ethanol/oil based dosage form earlier reported in US patent no. 4, 388, 307 has been performed in healthy human volunteers and reported in US patent no. 5,342, 625. Bio-availability level of 149.0% (± 48) is recorded for composition I as compared to composition X (for which bio-availability achieved is set as 100%). The mean AUC levels from composition I were 40% higher when compared to those from composition X but still had a high variation of 20%.

[0023] Some of the later U.S. Patents 5866159, 5916589, 5962014, 5962017, 6007840 and 6024978 also pertain

to oil-in-water microemulsion compositions having particle size less than 2000Å.

Although the compositions which yield oil-in-water microemulsions show much better bioavailability and reduced variability, the requirement to convert drug into micro emulsion form utilizes very high concentrations of surfactants like polyoxyethylene hydrogenated castor oil. Such surfactants are known to cause toxicity problems like nephrotoxicity, fat embolism and anaphylactic reactions (Ref. : Handbook of Pharmaceutical Excipients, Second Edition, Eds. Ainley Wade and P.J. Weller, The Pharmaceutical Press, 1994, p. 371 - 374). Moreover high amounts of surfactants unnecessarily increases the cost of the product.

[0024] The compositions of the European Patent Application no. 0985412 which describes micellar solubilization of Cyclosporin also suffer from similar disadvantages.

[0025] Alcohol is an essential part of most of the marketed compositions as is evident from the products available in the market (Sandimun [US Pat. No. 4, 388, 307] and Neoral [US Pat. No. 5,342, 625]) both of which contain Alcohol. Such compositions suffer from severe drawback of instability due to evaporation of a low boiling solvent like Alcohol. This is particularly true as the products are used in home environment, which cannot be precisely controlled with respect to temperature. Although very expensive cumbersome technology (such as cold formed Aluminium/ Aluminium Blister packs) is adopted to protect these products, yet the problem of instability is not completely solved. The stability problems are evident from strict storage conditions and usage requirements as declared either on the labels or package inserts of commercial products Sandimun, and Neoral drink solutions and capsules. Some of the examples are:

1. There is a requirement of storage of product below 30°C at the same time refrigeration is prohibited. This means that a patient using this product in a tropical country need to have an air-conditioned home environment. This is not only a limiting factor in use of this product but sometimes in economically backward countries it may not be possible that every person using the product has an air-conditioned storage area. Sometimes factors like prolong electricity failure and mechanical and electrical defects in air-conditioning system can cause instability problems to these products rendering them unstable for use.

2. There is also an a statement in Packing insert of Sandimun and Neoral drink solutions that " Sandimun Neoral solution should be used within 2 months of opening the bottle and be stored between 15° and 30°C, preferably not below 20°C for prolonged periods, as it contains oily components of natural origin which tend to solidify at low temperatures. A jelly-like formation may occur below 20°C, which is however reversible at temperatures up to 30°C. Minor flakes or a slight sediment may still be observed. These phenomena do not affect the efficacy and safety of the product, and the dosing by means of the pipette remains accurate. " indicating instability problems.

[0026] US Patent no. 5, 639, 724 discloses pharmaceutical compositions comprising Cyclosporin, transesterification product of a natural vegetable oil with glycerol which is exemplified in the specification as MAISINE (transesterification product of corn oil and glycerol) which is an essential component of the compositions. The cyclosporin must be mixed with a transesterfication product of a natural vegetable oil with glycerol. These compositions are not useful as drink solutions because of formation of jelly like lumps, since the transesterfication product is a jelly like substance at room temprature. Such composition also preferably require the use of alcohol. This compositions compares its bioavailability with that of older and inferior compositions based on US patent no. 4, 388, 307 and does not compare bioavailability with a more recently marketed compositions (NEORAL) as defined in US patent no. 5, 342, 625. US Patent No. 5,639,724 discloses the use of Labrafil as a preferred ingredient to be added to the composition of Cyclosporin and MAISINE for a drink solution. However, this patent does not address the problem of flake like substances formed by the presence of MAISINE even though Labrafil has been added to the composition.

[0027] The major consideration here is the accurate measurement of dose in Cyclosporin which is an essential feature because of the narrow therapeutic condition of the drug i.e. below threshold the organ rejection occurs and above a particular level the drug causes severe toxic reactions. The presence of jelly like substances or flakes make accurate dose measurement difficult.

Our attempts to formulate Cyclosporin containing significantly reduced amounts of surfactant like polyoxyethylene hydrogenated castor oil have surprisingly resulted in compositions which on dilution with water yield oil-in-water emulsion having very narrow globule size distribution and have an average globule size ranging between 200 - 600 nm (determined using Photon Correlation Spectroscopy). Further such compositions are also devoid of other drawbacks associated with compositions of prior art.

[0028] Composition of the present invention do not contain volatile solvents like alcohol.

The compositions are stable between wide range of temperature i.e. 15° - 45°C and do not congeal or flake at lower temperatures.

The drug is present in solubilised form after dilution and does not precipitate out.

[0029] The compositions are hydrophilic and can take upto 10% w/w of water without drug crystallizing out of solution. This is advantageous in soft gelatin capsules where migration of water from shell can cause precipitation of drug.

[0030] The compositions can be formulated as a drink solution or suitably encapsulated.
The compositions do not require specialized and costly packaging.
Further compositions of the present invention are also devoid of "lipophilic component" as described in the US Patents 5,342,625 and 5,741,512. This lipophilic component has been defined in the said patents as solvents which are devoid or substantially devoid of surfactant function and non-miscible with the selected hydrophilic phase. The compositions of the present invention are substantially devoid of such "lipophilic components" and hence also devoid of the defects associated with such fatty materials.

[0031] Compositions according to this invention may be formulated for oral administration including but not limited to drink solutions or formulated as hard or soft gelatin capsules.The capsules may be gelatin or cellulose capsules or two piece hard shell capsules. Drink solution formulations may be diluted with water or aqueous medium and the lipophilic Cyclosporin drug is maintained in a solubilized state, hence making the drug bioavailable in therapeutic concentrations.

[0032] Oral solution concentrates are to be diluted prior to intake and are used as start up therapies. These dosage forms provide more flexibility in dosage adjustments to achieve the optimum therapeutic concentrations as desired by the physicians. The second type of dosage forms are unit dosage forms for example capsules, generally soft or hard gelatin capsules or cellulose capsules or two piece hard shell capsules.

SUMMARY OF THE INVENTION

[0033] In accordance with the present invention there is described a homogenous substantially alcohol free, composition of Cyclosporin which comprises a Cyclosporin in a carrier medium comprising propylene glycol, esters of propylene glycol with C4 to C12 fatty acids and polyoxyethylene hydrogenated castor oils wherein the ingredients are present in the following range :

Cyclosporin A	1 - 25 %w/w
Propylene Glycol	2 - 70% w/w
Esters of propylene glycol with C4 to C12 fatty acids	15 - 60% w/w
Polyoxyethylene hydrogenated Castor oils	5 - 25% w/w

[0034] Wherein such compositions on dilution yield oil-in-water emulsions containing drug dissolved in the globules. The globules have average size within a narrow range of 200 - 600 nm.

DETAILED DESCRIPTION OF THE INVENTION

[0035] In accordance with the present invention there is described a homogenous substantially alcohol free, composition of Cyclosporin which comprises a Cyclosporin in a carrier medium comprising propylene glycol, esters of propylene glycol with C4 to C12 fatty acids and polyoxyethylene hydrogenated castor oils wherein the ingredients are present in the following range :

Cyclosporin A	1 - 25 %w/w
Propylene Glycol	2 - 70% w/w
Esters of propylene glycol with C4 to C12 fatty acids	15 - 60% w/w
Polyoxyethylene hydrogenated Castor oils	5 - 25% w/w

[0036] Wherein such compositions on dilution yield oil-in-water emulsions containing drug dissolved in the emulsion droplets or globules. The globules have average size within a narrow range of 200 - 600 nm.

[0037] The size distribution of one such composition (as per example 11) is shown in Fig. 1 which shows an average globule size of approximately 225 nm. The average globule size determined at different dilution levels is shown in Fig 2.

[0038] In another preferred embodiment of the invention the composition further comprises Triacetin or Glycerol triacetate. The glycerol triacetate may be present in the range of 0% to 10% w/w.

[0039] In another embodiment of the present invention the composition further comprises Oleic Acid in the range of 0 to 60% w/w. Oleic Acid may partially or completely replace the esters of propylene glycol with C4 to C12 fatty acids.
In another embodiment of the present invention the composition further comprises Antioxidants in the range of 0 to 5% w/w. The antioxidants can be selected from Butylated Hydroxy Anisole,Bytulated Hydroxy Toluene, Tocopherylacetate, d-α-tocopheryl polyethylene glycol 1000 succinate or a mixture thereof. Other antioxidants may also be used. The use of such compounds is only due to their antioxidant activity and they may not contribute as solvents for Cy-

closporin in the concentrations used.

[0040] In preferred embodiment of the invention is a composition comprising :

Cyclosporin	5 - 15 %w/w
Propylene Glycol	5 - 50% w/w
Esters of propylene glycol with C4 to C12 fatty acids	25 - 45% w/w
Polyoxyethylene hydrogenated Castor oils	10 - 20% w/w

[0041] In another embodiment of the invention the compositions are clear, stable, transparent, easily flowable and easily measurable at a wide range of temperature of 15° to 45°C.

[0042] The amount of all of the ingredients of the composition disclosed above equals to 100%.

[0043] The systems of the present invention are single phase systems. The expression "single phase" should be implied to mean a phase wherein the drug is solubilized using suitable blend of surfactant (s)/ co-surfactant (s).

[0044] The cyclosporins used in the compositions may be selected from cyclosporin A, cyclosporin D, cyclosporin G or any other known cyclosporin. It is preferred that cyclosporin A be used.

[0045] The composition can be incoporated into the capsule shells by conventional procedures as described in standard texts. ("The theory and practice of Industrial Pharmacy"by Leon Lachman et al. Third edition, LEA AND FEBIGER, USA).

[0046] The Soft Gelatin and two piece hard shell Capsules have a very distinct advantage of ease of carrying and administration as compared with oral solutions. These dosage forms hence contribute to a very large segment of commercial market. To aid the filling of the composition into two piece hard shell capsules suitable viscosity imparting agents known in the art, may be added. These may be selected from natural gums like Xanthan gum, Karaya gum, Guar gum, Acacia and the like or semi-synthetic or synthetic polymers like cellulosics e.g. hydrxypropyl cellulose. Hydroxypropylmethyl cellulose, Carboxy methyl cellulose; Acrylates like polymethyl methacrylic acid; carbomers like Carbopol 934, Carbopol 940 (BF Goodrich, USA); silicon dioxide.

[0047] Such compositions of the present invention which are solubilized systems and substantially free of C_{1-5} alkanols such as ethanol are distinctly advantageous over the ones described in US patent no. 5, 342, 625 with respect to manufacturing and distribution in the tropical countries.

[0048] It is most beneficial in context of hot tropical countries where loss of C_{1-5} alkanols such as ethanols are more due to evaporation.

[0049] Preferably the esters of propylene glycol with C4 to C12 fatty acids include mono-, di- or mono- and di- esters of propylene glycol with C4 to C12 fatty acids. Suitable products include propylene glycol laurate, propylene glycol dicaprylate/dicaprate, propylene glycol dioctanoate, propylene glycol monolaurate and the like. Especially suitable are the products commercially available under the trade names Lauroglycol, Neobee M-20, Capryol and Miglyol - 840.

[0050] Preferably the Polyoxyethylene hydrogenated castor oil is Polyoxyethylene 40 Hydrogenated Castor oil. Especially suitable is product available under the trade name Cremophor RH 40.

[0051] The term "easily measurable" has been used due to the characteristic features of the drug Cyclosporin. Cyclosporin requires accurate dose measurement because of its narrow therapeutic index. Most of the drink solution packs are provided with a pipette or a syringe for accurate dose measurement. This warrants that the solution is a sufficiently thin liquid to permit ease of measurement and not a semi solid mass and also it should be devoid of any flakes, jelly like formations or other sediments which can cause non-homogeneity in the dose. The composition of our invention possesses all the desired characteristics and hence is easily measurable as far as the dose requirements is concerned.

[0052] Compositions according to this invention may be formulated as drink solutions or diluted as a drink solution or formulated as soft gelatin capsules or as two piece hard shell capsules.

[0053] Several compositions as per this invention with different ranges of ingredients were subjected to commercial production trials and shelf-life stability studies and the inventors were successful in arriving at a composition which was easy to manufacture and stable for long periods of time when tested by accelerated stability studies.

[0054] Moreover when tested on healthy human volunteers, the composition(s) of this invention was found to have excellent bio-availability of Cyclosporin and were also found to be bioequivalent with commercial product. The comparative results are collected in Table I.

Table 1. :

Plasma concentration of Cyclosporine (ng/ml) following administration of a single oral dose of 2.5 mg/kg body weight. (Mean ± S.D.)			
Product	**Cmax**	**Tmax**	**AUC**
Neoral Mfd. By : Sandoz	723.21 ± 278.57	2.20 ± 0.40	3203.6 ± 1364.0
Composition as per Example 12.	668.32 ± 233.19	2.61 ± 0.38	3048.71 ± 1180.23

[0055] The invention will now be described with reference to the accompanying examples which should not be construed to limit the scope of the invention :

EXAMPLE 1 (PRIOR ART)

[0056]

	COMPONENT	AMOUNT
a)	Cyclosporin	100 mg (= ca. 10.5%)
b)	Maisine	550 mg (= ca. 57.8%)
c)	Labrafil M 2125	300 mg (= ca. 33.5%)
	TOTAL	950 mg

[0057] The mixture obtained was a semi-solid mass at room temperature suitable only for soft gelatin capsule formulation.

EXAMPLE 2 (PRIOR ART)

[0058]

	COMPONENT	AMOUNT
a)	Cyclosporin	100 mg (= ca. 10.5%)
b)	Maisine	490 mg (= ca. 52%)
c)	Labrafil M 2125	300 mg (= ca. 31.5%)
d)	Cremophore RH40	60 mg (= ca. 6.3%)
	TOTAL	950 mg

[0059] The mixture obtained was a semi-solid mass at room temperature suitable only for soft gelatin capsule formulation.

EXAMPLE 3 (PRIOR ART)

[0060]

	COMPONENT	AMOUNT
a)	Cyclosporin	100 mg (= ca. 10.5%)
b)	Maisine	850 mg (= ca. 52%)
	TOTAL	950 mg

[0061] The mixture obtained was a semi-solid mass at room temperature suitable only for soft gelatin capsule formulation.

EXAMPLE 4 (PRIOR ART)

[0062]

	COMPONENT	AMOUNT
a)	Cyclosporin	100 mg
b)	Propylene Glycol	200 mg
c)	Cremophore RH40	350 mg
d)	Labrafil M1944	200 mg
e)	Maisine	150 mg
	TOTAL	1000 mg

[0063] The composition obtained was a clear, homogenous liquid at a temperatures between 25° to 30°C, but at temperatures below 20°C jelly like flakes separated out.
Examples 5 to 15 relate to cyclosporin compositions of the present invention which can be used as a drink solution or can be suitably encapsulated.

Example 5

[0064]

Composition for two piece hard shell capsule	
Cyclosporin	- 10 g
Propylene Glycol	- 35 g
Cremophor RH 40	- 15 g
Propylene glycol laurate	- 40 g

[0065] Propylene Glycol was mixed with Cremophor RH 40 and heated upto 55 to 60°C and Cyclosporin was dissolved in the resultant. Propylene glycol laurate was then added to the bulk mixture and mixed. The resultant mixture was then filtered. The above composition may be filled in two piece hard shell capsules made up of materials like gelatin or cellulosics (e.g. Hydroxy propyl methyl cellulose based capsules like LICAPS ™) using suitably modified machines for filling liquids in two piece hard capsules. The capsules may be sealed using Qualiseal technology. The capsule shell may further comprise plasticizers, colorants, release modifiers, and the like.

Example 6

[0066]

Cyclosporin	- 10 g
Propylene Glycol	- 40 g
Cremophor RH 40	- 14 g
Propylene glycol dicaprylate/dicaprate	- 36 g

[0067] Propylene Glycol was mixed with Cremophor RH 40 and heated upto 55 to 60°C and Cyclosporin was dissolved in the resultant. Propylene glycol dicaprylate/dicaprate was then added to the bulk mixture and mixed. The resultant mixture was then filtered.

Example 7

[0068]

Cyclosporin	- 10 g
Propylene Glycol	- 40 g
Cremophor RH 40	- 15 g

(continued)

Propylene glycol dioctanoate	- 35 g

[0069] Propylene Glycol was mixed with Cremophor RH 40 and heated upto 55 to 60°C and Cyclosporin was dissolved in the resultant. Propylene glycol dioctanoate was then added to the bulk mixture and mixed. The resultant mixture was then filtered.

Example 8

[0070]

Cyclosporin	- 10 g
Propylene Glycol	- 40 g
Cremophor RH 40	- 10 g
Propylene glycol laurate	- 30 g
Propylene glycol dicaprylate/dicaprate	- 7 g
Triacetin	- 3 g

[0071] Propylene Glycol was mixed with Cremophor RH 40 and heated upto 55 to 60°C and Cyclosporin was dissolved in the resultant. Propylene glycol laurate was then added to the bulk mixture and mixed. To this was added propylene glycol dicaprylate/dicaprate followed by Triacetin. The resultant mixture was then filtered.

Example 9

[0072]

Cyclosporin	- 10 g
Propylene Glycol	- 40 g
Cremophor RH 40	- 10 g
Propylene glycol monolaurate	- 40 g

[0073] Propylene Glycol was mixed with Cremophor RH 40 and heated upto 55 to 60°C and Cyclosporin was dissolved in the resultant. Propylene glycol monolaurate was then added to the bulk mixture and mixed. The resultant mixture was then filtered.

Example 10

[0074]

Cyclosporin	- 10 g
Propylene Glycol	- 5 g
Cremophor RH 40	- 25 g
Propylene glycol monolaurate	- 30 g
Oleic Acid	- 27 g
Triacetin	- 2.93 g
Tocopheryl Acetate	- 0.07 g

[0075] Propylene Glycol was mixed with Cremophor RH 40 and heated upto 55 to 60°C and Cyclosporin was dissolved in the resultant. Propylene glycol monolaurate was then added to the bulk mixture and mixed. To this was added Oleic acid, Triacetin and Tocopherylacetate. The resultant mixture was then filtered.

Example 11

[0076]

Cyclosporin	- 10 g
Propylene Glycol	- 39.8 g
Cremophor RH 40	- 15 g
Propylene Glycol monolaurate	- 35 g
Tocopheryl acetate	- 0.2 g

[0077] Propylene Glycol was mixed with Cremophor RH 40 and heated upto 55 to 60°C and Cyclosporin was dissolved in the resultant. Propylene glycol monolaurate was then added to the bulk mixture followed by Tocopheryl acetate and mixed. The resultant mixture was then filtered. This composition when diluted with water yields dispersions having average globule size of approximately 225 nm. The globule size distribution curve is shown in Fig. 1 and the average globule size at different dilution levels is shown in Fig. 2.

Example 12

[0078]

Cyclosporin	- 10 g
Propylene Glycol	- 10 g
Cremophor RH 40	- 10 g
Oleic Acid	- 30 g
Propylene glycol monolaurate	- 38 g
Vitamin E TPGS	- 2 g

[0079] Propylene Glycol was mixed with Cremophor RH 40 and heated upto 55 to 60°C and Cyclosporin was dissolved in the resultant. Oleic Acid was then added to the bulk mixture and mixed. To this was added propylene glycol monolaurate and Vitamin E TPGS and mixed. The resultant mixture was then filtered.

Example 13

[0080]

Cyclosporin	- 10 g
Propylene Glycol	- 67 g
Cremophor RH 40	- 5.0 g
Propylene Glycol monolaurate	- 16 g
Tocopheryl acetate	- 2 g

[0081] Propylene Glycol was mixed with Cremophor RH 40 and heated upto 55 to 60°C and Cyclosporin was dissolved in the resultant. Propylene glycol monolaurate was then added to the bulk mixture followed by Tocopheryl acetate and mixed. The resultant mixture was then filtered.

Example 14

[0082]

Cyclosporin	- 10 g
Propylene Glycol	- 9 g
Cremophor RH 40	- 24 g
Propylene Glycol laurate	- 55 g
Tocopheryl acetate	- 2 g

[0083] Propylene Glycol was mixed with Cremophor RH 40 and heated upto 55 to 60°C and Cyclosporin was dissolved in the resultant. Propylene glycol laurate was then added to the bulk mixture followed by Tocopheryl acetate and mixed. The resultant mixture was then filtered.

Example 15

[0084]

Cyclosporin	- 10 g
Propylene Glycol	- 35 g
Cremophor RH 40	- 14 g
Propylene Glycol laurate	- 35.5 g
Tocopheryl acetate	- 0.5 g
Oleic acid	- 5 g

[0085] Propylene Glycol was mixed with Cremophor RH 40 and heated upto 55 to 60°C and Cyclosporin was dissolved in the resultant. Tocopheryl acetate was mixed with Oleic acid and added to Propylene glycol laurate with continuous stirring. This solution was then added to the drug solution and mixed. The resultant mixture was then filtered.

[0086] It is observed that all products obtained in the examples 6 to 10, and 12 to 15, provided upon dilution in a ratio from 1:250 to 1:1000, an average globule size in the specified range of from 200 to 600 nm, the preferred dilution medium being water.

[0087] With respect to the mixing step upon dilution it is further observed that any suitable method of mixing may be employed, an example being vortexing; nevertheless mixing simulating in vivo conditions is most preferred.

Claims

1. A homogeneous substantially alcohol free composition of cyclosporin which comprises cyclosporin A in a hydrophilic carrier medium comprising propylene glycol, esters of propylene glycol with C4 to C12 fatty acids and polyoxyethylene hydrogenated castor oils wherein the ingredients are present in the following range.

Cyclosporing A	1 - 25 % w/w
Propylene glycol	2 - 70 % w/w
Esters of propylene with C4 to C12 fatty acids	15 - 60 % w/w
Polyoxyethylene hydrogenated castor oils	5 - 25 % w/w

which composition, upon dilution with water, yields a stable, oil-in-water emulsion, whereof the oil phase consists of cyclosporin containing globules.

2. A composition as claimed in claim 1 wherein the ingredients are present in the following range:

Cyclosporing A	5 - 15 % w/w
Propylene glycol	5 - 50 % w/w
Esters of propylene with C4 to C12 fatty acids	25 - 45 % w/w
Polyoxyethylene hydrogenated castor oils	10 - 20 % w/w.

3. A composition according to claim 1 or 2, wherein said globules have an average size of from 200 to 600 nm.

4. A composition according to claims 1 to 3, wherein said globules have an average size of from 200 to 300 nm.

5. A composition as claimed in any of the preceding claims, which comprises esters of propylene glycol with C12 fatty acids.

6. A composition as claimed in any of the preceding claims, which further comprises glycerol triacetate or triacetin.

7. A composition as claimed in claim 6, wherein glycerol triacetate is present in the range 0 to 10 % w/w.

8. A composition as claimed in any of the preceding claims, further comprising oleic acid.

9. A composition as claimed in claim 8, wherein oleic acid is present in the range 0 to 60 % w/w.

10. A composition as claimed in any of the preceding claims, wherein the esters of propylene glycol with C4 to C12 fatty acids are partically or completely replaced with oleic acid.

11. A composition as claimed in any of the preceding claims, further comprising antioxidants.

12. A composition as claimed in claim 11, wherein the antioxidants are present in the range 0 to 5 %.

13. A composition as claimed in claim 11 or 12, wherein said antioxidants are chosen from the group comprising butylated hydroxy anisole, butylated hydroxy toluene, tocopherylacetate, d-α-tocopheryl polyethylene glycol 1000 succinate or a mixture thereof.

14. A composition according to any of the preceding claims, wherein said composition is diluted with water in a ratio from 1:250 to 1:1000.

15. A composition as claimed in any of the preceding claims, which can be formulated as a drink solution.

16. A composition as claimed in any of the preceding claims, which is free flowing at a temperature of 15 to 45°C.

17. Use of a composition according to any of the preceding claims for treating a cyclosporin indicated condition or symptom.

18. Use of a composition according to claim 17, wherein the cyclosporin indicated condition or symptom is T cell mediated immune process, allograft rejection, inflammation, or autoimmune conditions.

19. A composition claimed in any of the claims 1 to 16, which is used as a drink solution or incorporated into soft gelatin capsules or hard gelatin capsules or hard cellulose capsules or packed in a suitable device to affect measurable unit dosage dispending.

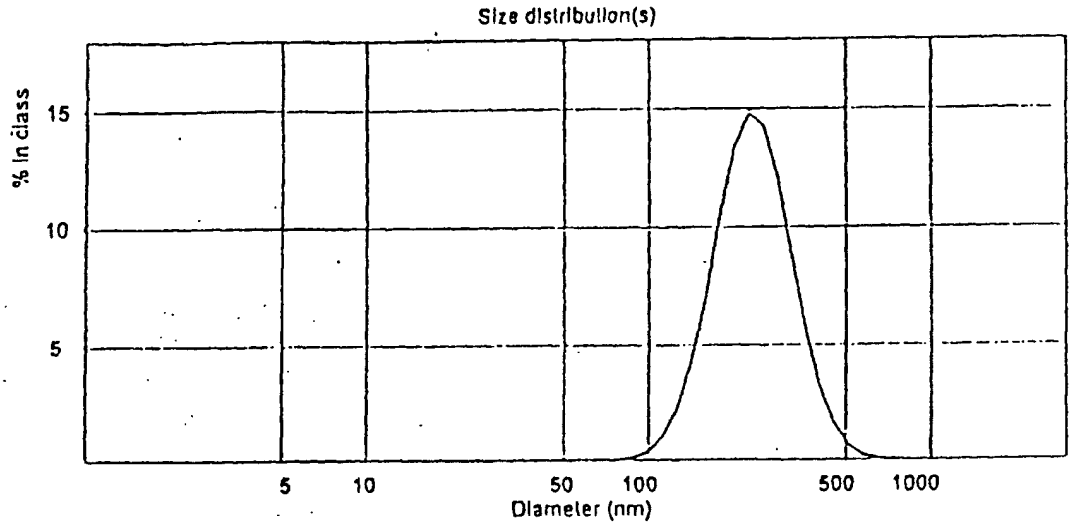
Example 11

DILUTION 1:500

Zetasizer 1000HS

Merit 46.1 % In range 98.6 %
Temperature 37.0 Viscosity 0.692 cP Angle 90.0 deg
RI medium 1.33 RI particle 1.46 + Abs. 0.00

Cumulant Z Ave 232.9 nm Polydispersity 0.099



Size (nm)	% Intensity	Size (nm)	% Intensity	Size (nm)	% Intensity
55.3	0.0	141.4	4.2	361.6	5.6
62.2	0.0	159.0	7.1	406.6	3.1
69.9	0.0	178.8	10.5	457.2	1.5
78.6	0.0	201.1	13.3	514.2	0.6
88.4	0.1	226.1	14.8	578.2	0.2
99.4	0.4	254.3	14.3	650.2	0.1
111.8	1.0	285.9	12.0	731.2	0.0
125.7	2.2	321.5	8.8	822.3	0.0

Peak : Mean 244.7 width 178.5 ,

Analysis Monomodal Fit 0.001243

Figure 1

Globule Size Determination of Cyclosporine Composition

as per Example 11

Dilution	Mean Globule Size(Z Ave.) (nm)	Polydispersity Index
1:500	232.9	0.0992
1:750	222.4	0.129
1:1000	231.3	0.141
1:1500	228.2	0.0727
1:2000	229.0	0.155
1:4000	224.6	0.0939
1:6000	211.8	0.002

Figure 2

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PARTIAL EUROPEAN SEARCH REPORT

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Application Number EP 00 20 1627

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	EP 0 985 412 A (PANACEA BIOTEC LTD) 15 March 2000 (2000-03-15) * see claims * ---	1-19	A61K38/13 A61K9/48 A61K9/107 A61P37/00
Y	EP 0 982 035 A (PANACEA BIOTEC LTD) 1 March 2000 (2000-03-01) * see abstract, claims 1-9, page 2 line 52 - page 3 line 6, page 5 lines 55-57 and page 7 lines 46-50 * ---	1-19	A61K47/10 A61K47/14 A61K47/44
Y	GB 2 228 198 A (SANDOZ LTD) 22 August 1990 (1990-08-22) * see claims and page 12 * -----	1-19	

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

A61K
A61P

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

Although claims 17-18 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Place of search	Date of completion of the search	Examiner
MUNICH	18 September 2000	Gore, V

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X: particularly relevant if taken alone
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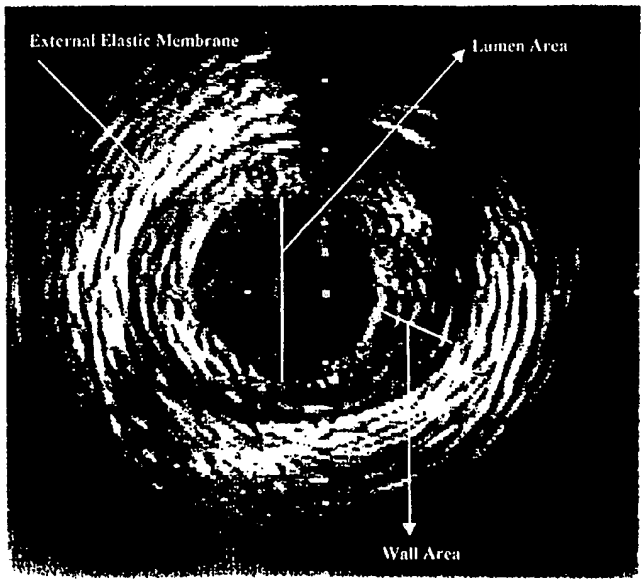
Without international search report and to be republished upon receipt of that report.

(54) Title: VASCULAR REMODELING AGENT



(57) Abstract

Probucol exerts a positive effect on vascular remodeling. By using probucol to promote vascular remodeling by the method of the invention, favorable results can be obtained in treating such diseases and conditions as restenosis following transluminal coronary angioplasty, intimal smooth muscle cell hyperplasia, vascular occlusion, or restenosis following transluminal angioplasty or atherectomy procedures performed on the coronary, iliac, femoral, renal or carotid arteries.

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VASCULAR REMODELING AGENT

This application is a continuation of U.S. Provisional Application 60/041,456 filed March 24, 1997.

INTRODUCTION AND BACKGROUND

Restenosis post-coronary dilation is a common disease of iatrogenic etiology that occurs as a direct consequence of arterial injury induced at the time of angioplasty. In the United States, over 500,000 coronary angioplasty procedures are performed annually and this number has been increasing steadily. Despite technical advances and multiple pharmacologic interventions, most studies have found that the incidence of angiographic restenosis remains in the range of 40%. The presenting symptom in the majority of patients with restenosis is exertional angina. Although clinical evidence for restenosis (MI, coronary revascularization, or recurrent angina) may vary from one study to another, clinical restenosis is generally seen in 25 to 35% of the patients within 6 months of their procedure (*Circulation* 1992; 86:100-110). Restenosis is a time-limited event. Serial angiographic follow-ups have shown that restenosis is most prevalent between 1 and 4 months and rarely occurs beyond 6 months after coronary angioplasty (*J Am Coll Cardiol* 1988; 12:616-23). The most common treatment strategy for restenosis is repeat angioplasty.

In the past decade, research on prevention of restenosis with pharmacological agents has been almost uniformly disappointing, except for some positive findings with a few drugs yielding conflicting results. The classes of agents tested in a placebo-controlled, randomized study have included antithrombotic agents, fish oil, calcium channel blockers, angiotensin-converting enzyme inhibitors, lipid-lowering agents, steroids, other antiproliferative agents, and magnesium.

Several studies have examined the efficacy of other methods of percutaneous revascularization in the prevention or the treatment of coronary restenosis. Such modalities include: directional and rotational atherectomy, excimer laser assisted angioplasty, cutting balloon angioplasty, heat generating angioplasty devices and coronary stenting.

Other than coronary stenting, no other percutaneous revascularization procedure offers demonstrated advantage over conventional PTCA in preventing or limiting recurring restenosis. Although stent implantation may, in some patients (de novo lesion, native coronary artery with a reference diameter larger than 3.0 mm) prove beneficial (*N Engl J Med* 1994; 331:489-495) (*N Engl J Med* 1994; 331:496-501), its clinical or angiographic superiority in vessels smaller than 3.0 mm in diameter has never been shown (*Semin Intervent Cardiol* 1996; 1:255-262).

Our understanding of the pathophysiology of restenosis has been steadily improving. Once believed to be initiated by an early thrombotic phenomenon, restenosis has been considered in the past 7 years essentially a proliferative process taking place in the weeks following angioplasty at the site of arterial injury. Cytologic analyses of post mortem and atherectomy samples have revealed that smooth muscle cells are the predominant cells responsible for this hyperplastic response. One

possible explanation for the negative results with the pharmacologic studies aimed at reducing neointimal hyperplasia is that these strategies targeted the wrong mechanism.

More recently, animal and clinical studies have begun to question the predominant role of cellular proliferation in restenosis and indicate that arterial remodeling is, in fact, an important aspect of the restenosis process (*Circulation* 1994; 89:2809-15). Inadequate vascular remodeling has been described not only after coronary balloon angioplasty but also after directional and rotational atherectomy and laser angioplasty (*Circulation* 1996; 94:35-43). Arterial remodeling is defined as a change in total arterial or external elastic membrane (EEM) cross-sectional area (CSA) over time. Arterial remodeling can be bi-directional. Adaptive positive arterial remodeling (an increase in arterial CSA) may represent a compensatory response of blood vessels to hemodynamic stress, arterial injury, and cellular proliferation. Adaptive arterial remodeling has first been described in early coronary artery atherosclerotic disease process (*N Engl J Med* 1987; 316:1371-5). Adaptive positive arterial remodeling in non-instrumented arteries prevents the reduction in lumen dimensions until plaque occupies 20% to 40% of the CSA within the internal elastic membrane (20% to 40% cross-sectional narrowing or plaque burden) (*Am J Cardiol* 1997; 80:1408-13). Alternatively, pathologic negative arterial remodeling (a decrease in arterial CSA or chronic arterial constriction) has been shown to contribute to lumen compromise in chronic, focal de novo stenosis in femoral and coronary arteries (*Circulation* 1995; 91:1444-9 and *Circulation* 1997; 95:1791-8).

SUMMARY OF THE INVENTION

This invention concerns methods and devices for promoting vascular remodeling. By the invention, vascular remodeling is accomplished by the systemic or local administration of the drug, probucol; 4,4'-[(1-methylethylidene)bis(thio)]bis-[2,6-bis(1,1-dimethylethyl)phenol]. The preparation of probucol has been described in US patent 3,576,883 and its use as a cholesterol lowering agent has also been described in US patent 3,5862,332. Its use to inhibit angiographic and clinical restenosis, i.e., death from cardiac cause, acute myocardial infarction, recurrence or exacerbation of angina pectoris and the need for revascularization (coronary bypass surgery or re-angioplasty) post-coronary angioplasty by promoting positive vascular remodeling has not previously been described. By using probucol to promote vascular remodeling by the method of the invention, favorable results can be obtained in treating diseases and conditions such as restenosis following balloon angioplasty, directional or rotational atherectomy, laser angioplasty and post-stent implantation. Promoting positive vascular remodeling would be favorable not only for interventions performed in the coronary arteries but also when these procedures are performed in any vascular structure, i.e., peripheral vessels (iliac, femoral etc.), renal, mesenteric, or carotid arteries, etc. Furthermore, promoting positive vascular remodeling would be favorable in the long-term treatment of patients with ischemic syndromes as seen in coronary artery disease, peripheral vascular disease, mesenteric vascular disease, cerebro-vascular disease, etc. The benefit of a positive vascular remodeling agent would

also be desirable for the treatment of conditions such as chronic arterial hypertension, post-heart transplant, post-bypass surgery, etc.

Five small clinical studies have suggested that probucol started before angioplasty may prevent restenosis (*Circulation* 1991; 84: II-299 (abstract), *Clin Ther* 1993; 15:374-382, *Jpn Heart J* 1996; 37:327-32, *Am Heart J* 1996; 132:23-29, *J Am Coll Cardiol* 1997; 30:855-62). Recently, we have shown in the MultiVitamins and Probucol (MVP) randomized clinical trial that probucol, a drug with strong antioxidant properties, given alone reduced angiographic lumen loss by 68%, restenosis rate per segment by 47% and the need for repeat angioplasty at 6 month by 58% compare to placebo. These results have been recently published (Multivitamins and probucol in the prevention of restenosis after coronary angioplasty: Results of the MVP randomized trial. *N Engl J Med* 1997, 365-372) and the publication is incorporated herein by reference. It was not possible to determine with angiography alone whether probucol acted via inhibition of tissue hyperplasia or improvement in vascular remodeling. Determination of this mechanistic question was necessary to help identify the appropriate targets in the periangioplasty period and, as taught by the present invention, lead to more effective strategies to prevent restenosis. In addition, the invention enables the skilled practitioner to use probucol in conjunction with other percutaneous coronary interventions such as stenting if it is deemed appropriate.

We have performed serial intravascular ultrasound (IVUS) examinations in a consecutive series of patients involved in the MVP trial. By providing tomographic views of coronary arteries with high resolution, IVUS allows quantitative assessment of changes in arterial lumen and wall dimensions. We were therefore able in this study to determine the pathophysiology of coronary restenosis after balloon angioplasty in patients systematically undergoing follow-up IVUS examination and determine the effect of probucol on tissue hyperplasia and vascular remodeling after coronary angioplasty.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will be further understood with reference to the drawings, wherein:

Figure 1 shows a tomographic section of a coronary artery (single frame of an IVUS study). The lumen area, the wall or plaque area and the external elastic membrane are identified.

Figure 2 represents the cumulative frequency curves of the lumen and EEM areas observed by intravascular ultrasound (IVUS) in all study groups.

Figure 3 shows the proportion of segments for each treatment group showing an increase in the external elastic membrane surface area between baseline and follow-up. Lower bars depict the proportion of segments showing a growth greater or equal to 1 mm^2.

Figure 4 shows the lag phase for LDL peroxidation for all four treatment groups at baseline, 1 month and 7 months post-treatment initiation.

DETAILED DESCRIPTION OF THE INVENTION

Study Design and Population

The present invention concerns the IVUS substudy from the MVP restenosis trial. MVP was a double-blind placebo-controlled randomized clinical trial with four study groups. The protocol was approved by the Montreal Heart Institute institutional review board. The MVP study design, inclusion and exclusion criteria have been previously described (*N Engl J Med* 1997, 365-372). Briefly, patients referred for elective coronary angioplasty were evaluated at least 30 days prior to their scheduled procedure. Eligible patients were asked to provide written informed consent. Patients were eligible if they were scheduled to undergo standard balloon angioplasty on at least 1 native coronary artery and had at least 1 de novo target lesion with luminal narrowing of 50% or more by caliper measurements.

Beginning 30 days prior to scheduled angioplasty, patients were randomly assigned to receive either probucol alone, multivitamins alone, the combination of probucol and multivitamins, or placebo. Probucol 500 mg or matched placebo was administered twice daily. The multivitamin complex, consisting of vitamin E 700 IU, vitamin C 500 mg and beta-carotene 30,000 IU, or matched placebo was also administered in one tablet twice daily. All patients received an extra dose of probucol 1000 mg and/or vitamin E 2000 IU and/or matched placebos 12 hours before angioplasty, according to randomization assignment. After angioplasty, all successfully dilated patients who did not present a periprocedural complication were maintained on their assigned study regimen until follow-up angiography was performed. All patients received aspirin 325 mg daily started at least 30 days before procedure and continued for the study period. Balloon angioplasty was performed according to standard techniques. Intracoronary nitroglycerin (0.3 mg) was given for each target artery for both pre- and post-dilatation angiography and at follow-up. The sequence of contrast injections with the exact degree of angulation was recorded and used for every angiogram. Coronary arteriograms (pre-, post-procedure, and final follow-up) were analyzed together using the Coronary Measurement System (CMS), as we have previously reported. Patient follow-up included clinical evaluation, exercise treadmill testing, blood chemistry, pill count and drug level measurements, and dietary assessment and intervention. Patients were readmitted for follow-up coronary angiography at 5 to 7 months. Patients in whom arteriography was performed for clinical reasons before the fifth month returned for repeat angiographic examination at 5 to 7 months if no definite angiographic restenosis was present on at least 1 dilated site. During follow-up, patients with recurrence or exacerbation of anginal symptoms were treated with medical therapy or revascularization procedures (reangioplasty or Coronary Bypass Surgery) as clinically indicated. Patients with angiographic restenosis (lesion > 50% at follow-up) without clinical evidence of ischemia were not subjected to further interventional procedures.

The MVP study was stopped prematurely by an independent monitoring board after 317

patients had entered the trial because one treatment had a significant effect on the primary (angiographic) efficacy endpoint. 111 patients underwent IVUS examination of the angioplasty site after final balloon inflation at baseline and constituted the initial population for the IVUS study.

IVUS Instrumentation and Examination

IVUS examinations were performed using 30 MHZ, 3.5 French mechanical (1800 rpm) ultrasound catheters (Boston Scientific, Natick, MA) and a dedicated imaging console (Hewlett-Packard, Andover, MA) (*Curr Opin Cardiol* 1994; 9:627-633). In six patients, both examinations were performed using 20 MHZ, 3.5 French 64-element IVUS catheters (Endosonics, Pleasanton, CA). IVUS studies were first performed after coronary angioplasty (after final balloon inflation) and then after follow-up angiography (before any subsequent intervention) and were always preceded by administration of intracoronary nitroglycerin (0.3 mg). IVUS imaging was monitored by an experienced cardiologist, but the angioplasty operator was blinded to ultrasound results to avoid altering standard balloon angioplasty practice. The IVUS catheter was advanced distal to the dilated site to an easily recognizable landmark, most often a side branch, which was noted and used for follow-up IVUS examination. One angiographic view was recorded on videotape before beginning pullback of the IVUS catheter. Slow manual pullbacks (approximately 0.5 mm/sec) were performed up to the guiding catheter and the ultrasound images recorded onto 0.5 inch S-VHS videotape for off-line analysis, with a detailed running audio commentary describing the location of the ongoing IVUS interrogation including the angioplasty site. Simultaneous high-resolution fluoroscopic images were recorded on the IVUS imaging screen during pullbacks to constantly know the location of the IVUS transducer. The operator was allowed to pause at sites of interest (e.g., angioplasty site, side branches) and contrast injections were performed when necessary to identify major and selected minor side branches, to accurately define the position of the IVUS catheter in relation to the angioplasty site and to improve delineation of the lumen-intima interface. Gain settings were carefully optimized during the initial assessment and changed only if required due to suboptimal image quality.

Quantitative IVUS Measurements

All the IVUS images were interpreted by experienced technicians supervised by a cardiologist blinded to treatment assignment. The post-angioplasty and follow-up studies were analyzed side by side. Great care was taken to ensure that the same and correct anatomic slice was measured in both IVUS studies. The fluoroscopic and angiographic images and audio commentary were used to determine the axial location of the ultrasound transducer and of IVUS landmarks relative to the angioplasty site and to side branches. IVUS landmarks (side branches, veins, calcifications, fibrotic deposits) were used to allow matching of the anatomic slice in both studies using frame by frame review of the images. The anatomic cross-section selected for serial analysis was the one at the angioplasty site with the smallest lumen area at follow-up. The corresponding anatomic slice was then identified on the post-angioplasty study. The images were digitized and quantitative analysis performed using custom-developed software for geometric computations (NIH Image 1.59). Quantitative analysis consisted in measurements of lumen area and the area within the external

elastic membrane (EEM) (Figure 1). The external elastic membrane was defined as the border between the hypoechoic media zone and the surrounding echobright adventitia. Wall area was calculated as the difference between EEM and lumen areas. When the plaque encompassed the IVUS catheter, the lumen area was assumed to be the size of the catheter.

Measurement of the EEM area can be difficult in the presence of extensive calcifications, because of acoustic shadowing of deeper structures. Two strategies were used to circumvent this problem (*J Am Coll Cardiol* 1997; 29:268-274). Considering that coronary arterial cross-sections are relatively circular, extrapolation of the EEM level was directly performed when each arc of calcification at the selected site did not shadow more than 60 degrees of the adventitial circumference. In addition, study of the anatomic slices just proximal and just distal to a selected calcified site was also performed when necessary to escape the shadowing and to identify the EEM correctly.

Statistical Methods

Statistical analysis was performed for all patients who underwent both baseline and follow-up examinations. The same analyses were performed for compliant patients only (efficacy analysis). Measurements are reported as mean ± 1 SD. The relations between changes in lumen, wall and EEM areas within study groups were tested using least squares linear regression analyses and Pearson's correlation coefficients. IVUS measurements were analyzed between groups with a two-way analysis of covariance (Fleiss JL. The design and analysis of clinical experiments. New York: John Wiley and Sons, 1986; 186-194) on follow-up areas, controlling for post-angioplasty area and for potential prognostic factors and extracting treatment effects and interactions. The IVUS measurements were analyzed per segment by the generalized estimating equations (GEE) technique (*Biometrika* 1986; 73:13-22), which takes into account potential dependence between segments in the same patient.

Results

Of the 107 patients who underwent IVUS examination of the angioplasty site immediately after intervention, 11 were not studied at follow-up for different reasons. Two patients underwent both IVUS studies but extensive calcifications precluded quantitative IVUS measurements at the selected angioplasty site. Thus, 94 patients constituted our study population and were distributed in the four groups as follows: 21 received probucol alone, 25 multivitamins alone, 20 probucol plus multivitamins and 28 received only placebo. Selected demographic, clinical and angiographic characteristics of the 4 groups are shown in Table 1. There were no statistically significant baseline differences between study groups. Six patients were not adequately compliant to study medications (1, 2, 2 and 1 in the probucol, vitamins, combined treatment and placebo groups). There were also no baseline differences between groups when compliant patients only were evaluated.

Natural History of Restenosis: IVUS Results in the Placebo Group

Table 2 summarizes IVUS results for the placebo alone group and for the 3 active treatment groups. At baseline (immediately after angioplasty) in the placebo group, lumen, wall and EEM areas

TABLE 1: BASELINE DEMOGRAPHIC, CLINICAL AND ANGIOGRAPHIC CHARACTERISTICS OF THE FOUR STUDY GROUPS

	Placebo Alone	Vitamins Alone	Probucol + Vitamins	Probucol Alone
Patients	28	25	20	21
Age (yrs)(means ± SD)	59.5 ± 8.8	58.1 ± 11.1	57.1 ± 8.9	56.1 ± 7.8
Female (%)	28.6	8.0	30.0	9.5
Ever Smoked (%)	17.9	8.0	25.0	4.8
Current Smoker (%)	7.1	28.0	15.0	19.1
Hist. of Diabetes (%)	7.1	0	20.0	20.0
Hist. of Hypertension (%)*	42.9	52.0	50.0	14.3
CCS angenia class (%)				
I	0	4.0	10.0	14.3
II	53.6	56.0	65.0	66.7
III	28.6	24.0	10.0	14.3
IV	0	0	0	0
Prior MI (%)	32.1	52.0	50.0	52.4
Prior CABG (%)	7.1	0	5.0	0
Prior PTCA (%)	7.1	8.0	15.0	4.8
No. of Diseased Vessels (%)				
1	39.3	36.0	45.0	33.3
2	39.3	48.0	25.0	42.9
3	21.4	16.0	30.0	23.8
Target Vessels (%)				
Left anterior descending	54.8	56.7	33.0	40.0
Left circumflex	16.1	20.0	24.0	36.0
Right coronary artery	29.0	23.3	32.0	24.0
Maximum pressure (mean ± SD)	10.8 ± 2.2	10.8 ± 3.2	10.3 ± 2.7	10.1 ± 2.1
Total Inflation Time (sec)	513 ± 236	496 ± 205	438 ± 209	516 ± 277
Balloon to Artery Ratio	1.04 ± 0.17	1.02 ± 0.10	1.06 ± 0.22	1.09 ± 0.11

CABG: Coronary artery bypass graft
MI: Myocardial infraction
PTCA: Percutaneous transluminal coronary angioplasty

* p = 0.042 based on Chi-squared test

TABLE 2: SERIAL INTRAVASCULAR ULTRASOUND RESULTS*

	Placebo Alone (n = 31)	Vitamin Alone (n = 30)	Probucol & Vitamins (n = 25)	Probucol Alone (n = 25)	p value Probucol vs. No Probucol	p Value Vitamins vs. No Vitamins
After Angioplasty						
Lumen area (mm^2)	4.52 ± 1.39	4.08 ± 1.41	4.10 ± 0.95	4.62 ± 1.59	0.7885	0.0544
EEM area (mm^2)	13.37 ± 3.45	13.17 ± 3.90	11.21 ± 3.25	12.20 ± 4.66	0.0261	0.4258
Wall area (mm^2)	8.85 ± 3.01	9.09 ± 3.28	7.11 ± 2.75	7.57 ± 3.98	0.0071	0.8930
Follow-up						
Lumen area (mm^2)	3.31 ± 1.44	3.24 ± 1.58	3.85 ± 1.39	4.47 ± 1.93	0.0022	0.8449
EEM area (mm^2)	13.66 ± 4.18	13.26 ± 3.80	12.37 ± 3.70	13.93 ± 4.74	0.0055	0.3590
Wall area (mm^2)	10.35 ± 3.95	10.02 ± 3.40	8.52 ± 3.49	9.46 ± 4.36	0.2739	0.1795
Follow-up-Post PTCA						
Lumen area (mm^2)	-1.21 ± 1.88	-0.83 ± 1.22	-0.25 ± 1.17	-0.15 ± 1.70	0.0022	0.8449
EEM area (mm^2)	0.29 ± 2.93	0.09 ± 2.33	1.17 ± 1.61	1.74 ± 1.80	0.0055	0.3590
Wall area (mm^2)	1.50 ± 2.50	0.93 ± 2.26	1.41 ± 1.45	1.89 ± 1.87	0.2739	0.1795

* Per segment analysis using the GEE technique

were 4.52 ± 1.39 mm^2, 8.85 ± 3.01 mm^2, and 13.37 ± 3.45 mm^2, respectively. At follow-up, these values were 3.31 ± 1.44 mm^2, 10.35 ± 3.95 mm^2, and 13.66 ± 4.18 mm^2. Thus, lumen area at follow-up decreased by -1.21 ± 1.88 mm^2, and wall and EEM areas increased by 1.50 ± 2.50 mm^2 and 0.29 ± 2.93 mm^2. The change in lumen area correlated more strongly with the change in EEM area r = 0.53, p = 0.002) than with the change in wall area r = -0.13, p = 0.49).

Effects of Probucol and Vitamins on Tissue Hyperplasia and Vascular Remodeling: IVUS Results in the Four Study Groups

Lumen area at follow-up was 3.31 ± 1.44 mm^2 in the placebo group, 3.24 ± 1.58 mm^2 for vitamins only, 3.85 ± 1.39 mm^2 for combined treatment and 4.47 ± 1.93 mm^2 for probucol alone (p = 0.002 for probucol versus no probucol; p = 0.84 for vitamins versus no vitamins). Follow-up wall area was 10.35 ± 3.95 mm^2 for the placebo group, 10.02 ± 3.40 mm^2 in the vitamins only group, 8.52 ± 3.49 mm^2 for combined treatment and 9.46 ± 4.36 mm^2 for probucol alone (p = 0.27 for probucol versus no probucol and 0.18 for vitamins versus no vitamins). EEM area at follow-up was 13.66 ± 4.18 mm^2 in patients receiving placebo alone, 13.26 ± 3.80 mm^2 for vitamins only, 12.37 ± 3.70 mm^2 for combined treatment and 13.93 ± 4.74 mm^2 for those treated with probucol only (p = 0.005 for probucol versus no probucol; p = 0.36 for vitamins versus no vitamins). Figure 2 represents the cumulative frequency curves of the lumen and EEM areas observed on IVUS in all study groups.

Lumen loss was 1.21 ± 1.88 mm^2 in the placebo group, 0.83 ± 1.22 mm^2 for vitamins alone, 0.25 ± 1.17 mm^2 for combined treatment and 0.15 ± 1.70 mm^2 for patients receiving probucol alone (p = 0.002 for probucol versus no probucol and p = 0.84 for vitamins versus no vitamins). The change in wall area was 1.50 ± 2.50 mm^2, 0.93 ± 2.26 mm^2, 1.41 ± 1.45 mm^2 and 1.89 ± 1.87 mm^2, respectively (p = NS). EEM area increased at follow-up by 0.29 ± 2.93 mm^2 in the placebo group, 0.09 ± 2.33 mm^2 in the vitamins only group, 1.17 ± 1.61 mm^2 for combined treatment and 1.74 ± 1.80 mm^2 for the probucol alone group (p = 0.005 for probucol versus no probucol and p = 0.36 for vitamins versus no vitamins). An increase in EEM area of at least 1 mm^2 at follow-up occurred in 38.7% of patients given placebo alone, in 23.3% in the vitamins only group, 44.0% in the combined treatment group, and 72.0% of patients taking probucol (Figure 3). Table 3 shows the changes in lumen, wall and EEM areas for compliant patients only.

There was no statistically significant drug interaction in the factorial design. However, considering potential underpowering to detect such an interaction, post-hoc analyses comparing each group separately and adjusted for a possible interaction were performed. Results remained significant for all ultrasound endpoints between the probucol alone and placebo groups.

Probucol is one of the first pharmacological interventions shown to prevent coronary restenosis after balloon angioplasty. However, its mechanism of action and its efficacy as a vascular remodeling agent has never been studied. In the MVP study, probucol therapy initiated 30 days before and given alone for 6 months after angioplasty resulted in reductions, of 68% in angiographic lumen loss, 47% in restenosis rate per segment and 58% in the need for repeat angioplasty when

TABLE 3: EFFICACY ANALYSIS IN COMPLIANT PATIENT

	Placebo Alone (n = 30)	Vitamins Alone (n = 28)	Probucol & Vitamins (n = 23)	Probucol Alone (n = 25)	p value Probucol vs. No Probucol	p Value Vitamins vs. No Vitamins
Follow-up-Post PTCA						
Δ Lumen area (mm^2)	-1.04 ± 1.67	-0.78 ± 1.25	-0.25 ± 1.20	-0.07 ± 1.69	0.0020	0.5605
Δ EEM area (mm^2)	0.48 ± 2.77	0.10 ± 2.23	1.15 ± 1.60	1.88 ± 1.69	0.0034	0.1989
Δ Wall area (mm^2)	1.52 ± 2.54	0.89 ± 2.15	1.40 ± 1.31	1.95 ± 1.88	0.2179	0.1345

compared to placebo. Whether probucol acted via prevention of tissue hyperplasia, improvement in vascular remodeling, or both, could not be adequately addressed by angiography and required the use of IVUS. It was necessary to determine the mechanism of action of probucol in order to developbetter strategies against restenosis. These strategies are unequivocally needed. Indeed, although probucol drastically reduced angiographic lumen loss in the MVP study, restenosis still occurred in over 20% of patients given probucol alone. Furthermore, the positive results found with stents have predominantly been obtained in patients with large coronary arteries, i.e., 3.0 mm in diameter or more (*N Engl J Med* 1994; 331:489-495, *N Engl J Med* 1994; 331:496-5). In a subset analysis of patients randomized in the BENESTENT trial and having interventions performed on small vessels (< 3.0 mm), the benefits noted in the patients with larger vessels (> 3.0 mm) were not seen (*Semin Intervent Cardiol* 1996; 1:255-262). In the stented population, smaller vessel size was associated with a higher stent/vessel ratio, a greater relative gain and a greater subsequent loss index, and a higher risk of adverse cardiac events within six months of the procedure.

Before learning how probucol acted in the MVP study, it was first necessary to clarify the mechanisms of lumen loss and restenosis after balloon angioplasty in the placebo group. In these control patients, the increase in wall area (mean: 1.50 mm^2) was greater than the decrease in lumen area (-1.21 mm^2), with a slight increase of the EEM area (0.29 mm^2). However, the change in lumen area correlated better with the change in EEM area than with the change in wall area. Taken together, these results indicate that the direction (enlargement [positive] or constriction [negative]) and extent (e.g., inadequate or adequate compensatory enlargement) of vascular remodeling in response to the tissue hyperplasia that occurs after balloon angioplasty determine the magnitude of lumen loss at follow-up. Animal studies have yielded various results on the relative importance of remodeling and tissue hyperplasia in the pathogenesis of restenosis. Animal models, however, have different proliferative and thrombogenic responses to arterial trauma, and plaque content is often significantly different than what is found in human atherosclerotic stenoses requiring angioplasty. One additional limitation is that wall and EEM (or internal elastic lamina) areas were never measured serially with the same method in a given animal artery.

Although clinical studies have revealed that remodeling occurs in humans after different interventions, relative changes in wall and EEM areas have varied. Mintz et al observed that 73% of late lumen loss after intervention was explained by a decrease in EEM area (*Circulation* 1996; 94:35-43). As acknowledged by the authors, however, the study involved a mix of primary and restenotic lesions on which different interventions were performed. Balloon angioplasty was performed alone in only a small minority of patients, and follow-up examination was largely driven by the presence of symptoms. An underestimation of the increase in plaque area may also have occurred because of the larger acoustic size (i.e., physical catheter size + central artifact) of the catheters that were used in that study. Preliminary data from the SURE study now appear to show that most of the lumen loss from immediately after to 6 months after balloon angioplasty (-1.51 mm^2) was not caused by a decrease in EEM area (-0.46 mm^2) (*J Am Coll Cardiol* 1996; 27:41A).

Whereas data from this and other studies support the conclusion that lumen loss after balloon angioplasty is caused by the combination of inadequate or deleterious vessel remodeling and tissue hyperplasia, probucol in the MVP study significantly reduced lumen loss by improving vascular remodeling but it did not modify the post-angioplasty increase in wall area. When compared to non-probucol treated patients, those receiving probucol showed a reduction in lumen loss by 80% or 0.79 mm^2 when assessed by IVUS. When compared to the placebo group only, the reduction in lumen loss with probucol given alone was 88% or 1.06 mm^2. A striking improvement in compensatory vessel enlargement was responsible for probucol's favorable effect on lumen loss. There was an enlargement in EEM area of 1.74 mm^2 from immediately after angioplasty to follow-up in patients treated with probucol alone compared with 0.29 mm^2 in patients given placebo. This represents a 730% increase in vessel enlargement in patients given probucol only. Five other clinical studies, smaller than MVP, have also observed the antirestenotic effect of probucol using angiography (*Circulation* 1991; 84:II-299 (abstract), *Clin Ther* 1993; 15:374-382, *Jpn Heart J* 1996; 37:327-32, *Am Heart J* 1996; 132:23-29, *J Am Coll Cardiol* 1997; 30:855-62). In addition, a better arterial response after balloon injury has been demonstrated with probucol in animal studies (*Circulation* 1993; 88:628-637, *Proc Natl Acad Sci* 1992; 89:11312-11316). Other antioxidants were also specifically shown in animals to improve vascular remodeling after angioplasty (*Arterioscle Thromb Vasc Biol* 1995; 15:156-165). Thus, results from the MVP trial and from these other studies provide strong support for the central role of oxidative processes in the pathophysiology of restenosis.

Oxygen free radicals generated by damaged endothelium, activated platelets and neutrophils at the angioplasty site (*Mayo Clin Proc* 1988; 63:381-389) can induce chain reactions which result in endothelial dysfunction (*Nature* 1990; 344:160-162) and LDL oxidation (*N Engl J Med* 1989; 320:915-924). Macrophages activated by oxidized LDL and dysfunctional endothelium can then release several cytokines and growth factors promoting matrix remodeling and smooth muscle cell proliferation. Matrix degradation by metalloproteinases precedes or accompanies early formation of new extracellular matrix (*Circ Res* 1994; 75:650-658) after angioplasty and also is a crucial step before smooth muscle cell migration and proliferation (*Circ Res* 1994; 75:539-545, *Biochem J* 1992; 288:93-99). Interestingly, it has recently been shown that oxygen free radicals can modulate matrix remodeling by activating metalloproteinases (*J Clin Invest* 1996; 98:2572-2579). The same events that lead to an increase in wall area after angioplasty, i.e., matrix formation and smooth muscle cell proliferation, are likely involved in the process of vascular remodeling. Smooth muscle cell contraction (*Crit Care Med* 1988; 16:899-908), along with cross-linking of collagen fibers (*J Am Coll Cardiol* 1995; 25:516-520), may limit compensatory vessel enlargement in response to tissue hyperplasia and may even result in vascular constriction. Again, nonenzymatic cross-linking of collagen typically involves oxidation processes (FASEB J 1992; 6:2439-2449). In addition, chronic flow-dependent changes in vessel size may be limited by endothelial dysfunction (*Science* 1986; 231:405-407).

Not being bound by any theory, the powerful chain-breaking antioxidant effects of probucol (*Am J Cardiol* 1986; 57:16H-21) may have prevented endothelial dysfunction (*J Lipid Res* 1991; 32:197-204, *N Engl J Med* 1995; 332:488-493), LDL oxidation (*J Clin Invest* 1986; 77:641-644) and macrophage and metalloproteinase activation in the MVP study. This could have limited smooth muscle cell activation, migration, proliferation and contraction, and matrix degradation and deposition of new collagen and other fibers. By ultimately limiting smooth muscle cell contraction, collagen formation and cross-linking, and endothelial dysfunction through its antioxidant effects, probucol can modify vascular remodeling and allow greater vessel enlargement. The hypocholesterolemic effect of probucol is weak and unlikely by itself to be responsible for the positive MVP results. However, specific inhibition by probucol of secretion of interleukin-1 (*Am J Cardiol* 1988; 62:77B-81B) may have decreased secretion of metalloproteinases (*Circ Res* 1994; 75:181-189) and modified matrix remodeling.

Similar to what we observed clinically and angiographically, multivitamins had no significant effect on IVUS endpoints. It is not clear why multivitamins did not prevent restenosis whereas probucol did. Dietary intervention and smoking habits were similar in all groups. Probucol may simply be a more powerful antioxidant than the combination of vitamins. To this regard, preliminary results from the continuous spectrophotometric monitoring of diene conjugates in LDL after the addition of copper ions to the isolated lipoprotein ex vivo (*Free Radic Res Commun* 1989; 6:67-75) of MVP patients are noteworthy. Figure 4 shows the lag phase for LDL peroxidation for all four treatment groups at baseline, 1 month and 7 months post-treatment initiation. Although LDL trapped in the arterial intima encounters a very complex environment, compared with the simple set-up of oxidation resistance assays, our results would suggest that probucol treatment for one month provided a significantly greater protection against LDL oxidation than vitamins alone or the combination of probucol and vitamins. Although the described (*Science* 1984; 224:569-73) pro-oxidant effects of high doses of multivitamin was not evident ex vivo in the vitamins alone group, it does not exclude the possibility that it may have played a role in vivo. Alternatively, the effect of probucol on interleukin-1 and on reverse cholesterol transfer may have contributed to this result.

Lumen loss after balloon angioplasty is shown to be due to inadequate vessel remodeling in response to tissue hyperplasia. We have shown using IVUS that probucol exerts its antirestenotic effects in humans by improving vascular remodeling after angioplasty. The disclosure describes the positive vascular remodeling effects of probucol using the balloon angioplasty procedure as an example. Probucol, the first pharmacologic agent demonstrated to have positive vascular remodeling capabilities, or any other similar agent to be described in the future for that matter, would be useful in a variety of clinical conditions associated with arterial wall injury. Such conditions could be of natural origin or iatrogenic. More specifically, natural conditions may include hypertensive disorders, vascular disorders affecting the coronaries, the peripheral arteries, the cerebral arteries, the pulmonary arteries, the vascular supply to the kidneys, and any other organ in the abdominal cavity, etc. Iatrogenic conditions for which probucol or a positive vascular remodeling agent may be

beneficial could include conditions such as post-coronary intervention, i.e., balloon angioplasty, directional or rotational atherectomy, laser assisted angioplasty, post-radiation therapy, or coronary stenting or any other intervention which may be associated with vascular injury which will lead to intimal proliferation or negative vascular remodeling (constriction). The potential benefit of a positive vascular remodeling agent would not be limited to the coronary tree. Similar vascular injury in the renal, carotid, vertebral, mesenteric, peripheral vascular bed would also benefit from such an agent. In other conditions, such as post-bypass surgery, the conduit utilized for bypass (vein or artery) would also benefit from a vascular remodeling agent. Such an agent could favor the development (growth) of the graft immediately post-surgery and/or prevent its occlusion due to intimal hyperplasia or atherosclerotic process. Patients with renal failure treated with hemodialysis through an arterio-venous fistula frequently show intimal proliferation and progressive disease of their shunt, which eventually will occlude. Vascular remodeling agent may be beneficial and prolong the life of the shunt. Post-organ transplant, vascular damage and intimal proliferation, which may lead to vascular obstruction and graft damage, is a frequent problem that may also benefit from the use of a vascular remodeling agent. In addition, vascular remodeling agent could play a role in the treatment of patients with a condition such as primary pulmonary hypertension.

So far, the invention and its applications have only been described for the vascular system. It is intended to encompass with these claims the use of such an agent for any condition where a structure surrounded by a muscular wall will benefit from having its wall remodeled (expansion) so doing creating a larger conduit or cavity.

Probucol or the agent with positive vascular remodeling properties could be administered systemically or locally. Systemic administration may be accomplished with intra-venous/intra-arterial injection (bolus injection or longer perfusion) orally (any forms of oral delivery systems), subcutaneously (injection, pallet, slow release, etc), per-cutaneously (patch, cream, gel, etc.) with short acting or long acting (slow release) delivery profile. A local delivery system would include any device intended to locally delivery probucol or a similar agent (i.e., local delivery catheter, coated or impregnated stent, local infusion device, etc.).

Further variations and modifications will be apparent to those skilled in the art and are intended to be encompassed by the claims appended hereto.

WHAT IS CLAIMED IS:

1. A method of preventing or treating hyperproliferative vascular disease through vascular remodeling in a susceptible mammal, comprising:

administering to said mammal an amount of probucol, similar compound or derivative or a pharmaceutically acceptable salt thereof, effective in compensating for smooth muscle proliferation and intimal thickening by promoting vascular remodeling in said mammal.

2. The method of claim 1, wherein the drug delivery is accomplished by oral, parenteral, intravascular, intro-muscular, intranasal, intrabronchial, transdermal, rectal administration, or via local delivery of the drug with a local delivery system (passive or active) or with a drug impregnated vascular stent or other device slowly delivering the drug locally.

3. The method of claim 1, wherein the probucol, similar compound or derivative or a pharmaceutically acceptable salt thereof is administered prior to and/or concurrent with said mammal undergoing a percutaneous transluminal coronary angioplasty procedure.

4. The method of claim 3, which further comprises administering the probucol, similar compound or derivative or a pharmaceutically acceptable salt thereof subsequent to said mammal undergoing a percutaneous transluminal coronary angioplasty procedure.

5. The method of claim 1, wherein the hyperproliferative vascular disease is selected from the group consisting of intimal smooth muscle cell hyperplasia, restenosis, atherosclerotic plaque and vascular occlusion secondary to other mechanisms.

6. The method of claim 5, wherein the hyperproliferative vascular disease is restenosis.

7. The method of claim 1, wherein the probucol, similar compound or derivative or a pharmaceutically acceptable salt thereof is administered prior to, concurrent with and/or subsequent to said mammal undergoing a procedure which is a member selected from the group consisting of transluminal angioplasty, balloon angioplasty, directional atherectomy, rotational atherectomy, laser assisted angioplasty, post radiation therapy, coronary stenting, bypass surgery and organ transplant.

8. The method of claim 1, wherein the probucol, similar compound or derivative or a pharmaceutically acceptable salt thereof, is administered prior to, concurrent with and/or subsequent to said mammal sustaining a biologically mediated vascular injury.

9. The method of claim 1, wherein the probucol, similar compound or derivative or a

pharmaceutically acceptable salt thereof is administered prior to, concurrent with and/or subsequent to said mammal sustaining a mechanically mediated vascular injury.

10. A sustained release device for releasing probucol to improve vascular remodeling comprising probucol, similar compound or derivative or a pharmaceutically acceptable salt thereof in a form that is consistently and progressively released from a device over a certain period of time when implanted in or near a blood vessel.

11. The sustained release device of claim 10, wherein the device is in the form of a stent.

12. A local delivery device for releasing probucol to promote vascular remodeling comprising probucol, similar compound or derivative or a pharmaceutically acceptable salt thereof in a form that is released from a device when temporarily positioned or permanently implanted in or near a blood vessel.

13. The local delivery device of claim 12, wherein the device is in the form of a local delivery or infusion catheter, a coated or impregnated stent or any other endovascular device allowing local infusion.

14. The method of claim 1, wherein the probucol, similar compound or derivative or a pharmaceutically acceptable salt thereof is administered for treatment of a injury to a vasculature selected from the group consisting of the coronary tree, carotid artery, vertebral artery, iliac artery, femoral artery, renal artery, the thoracic and abdominal aorta and its branches, mesenteric, pulmonary, and peripheral vascular bed.

15. A method of treatment for the expansion of a muscular wall of a mammal, comprising:

administering to said mammal in need of muscular wall expansion an effective amount of probucol, similar compound or derivative or a pharmaceutically acceptable salt thereof.

16. A method of promoting positive vascular remodeling, comprising:

administering to said mammal in need thereof muscular wall expansion an effective amount of probucol, similar compound or derivative or a pharmaceutically acceptable salt thereof.

17. The method of claim 16 wherein the positive vascular remodeling is treatment for a condition selected from the group consisting of high blood pressure, pulmonary hypertension, post-organ transplant, progressive disease of an arterio-venous shunt and cardiac bypass surgery.

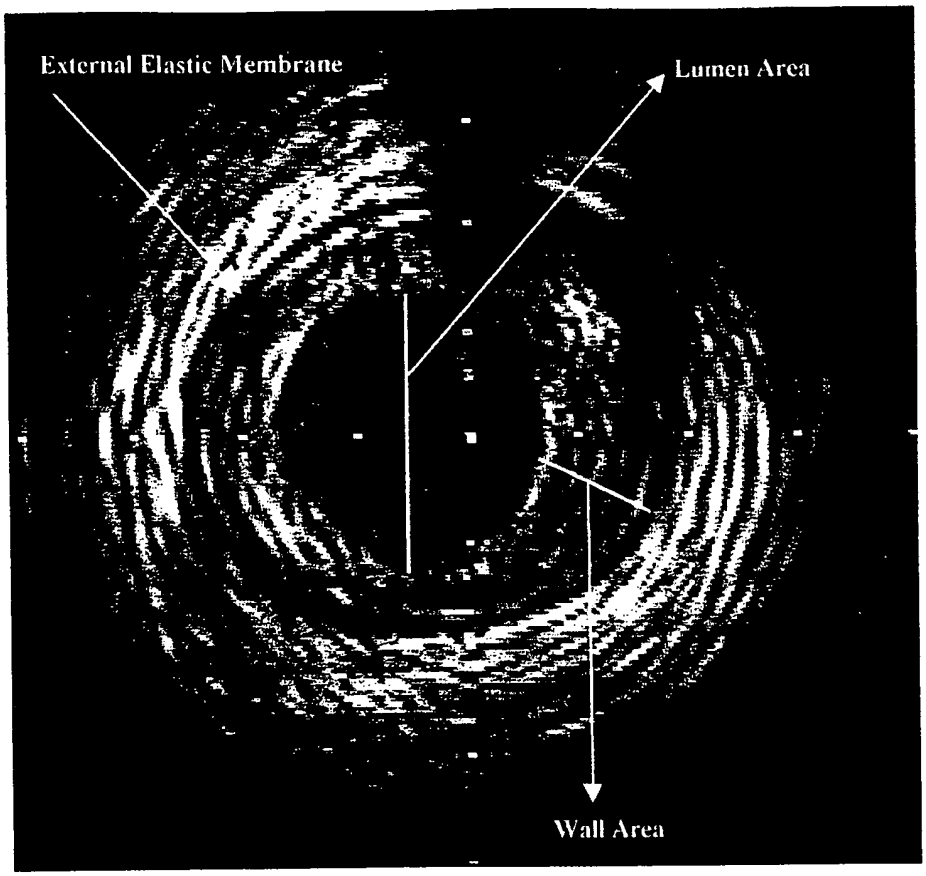
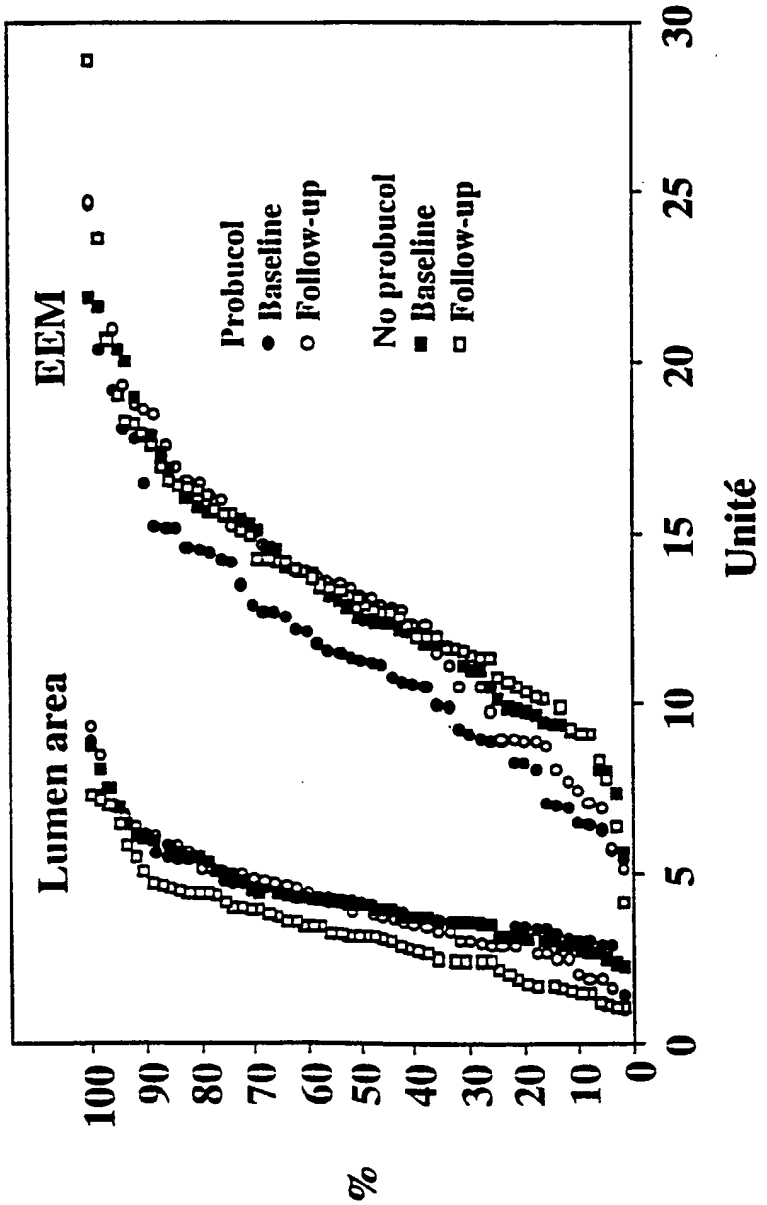


FIG. 1


EEM
Lumen area
Probucol
Baseline
Follow-up
No probucol
Baseline
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10
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FIG. 2

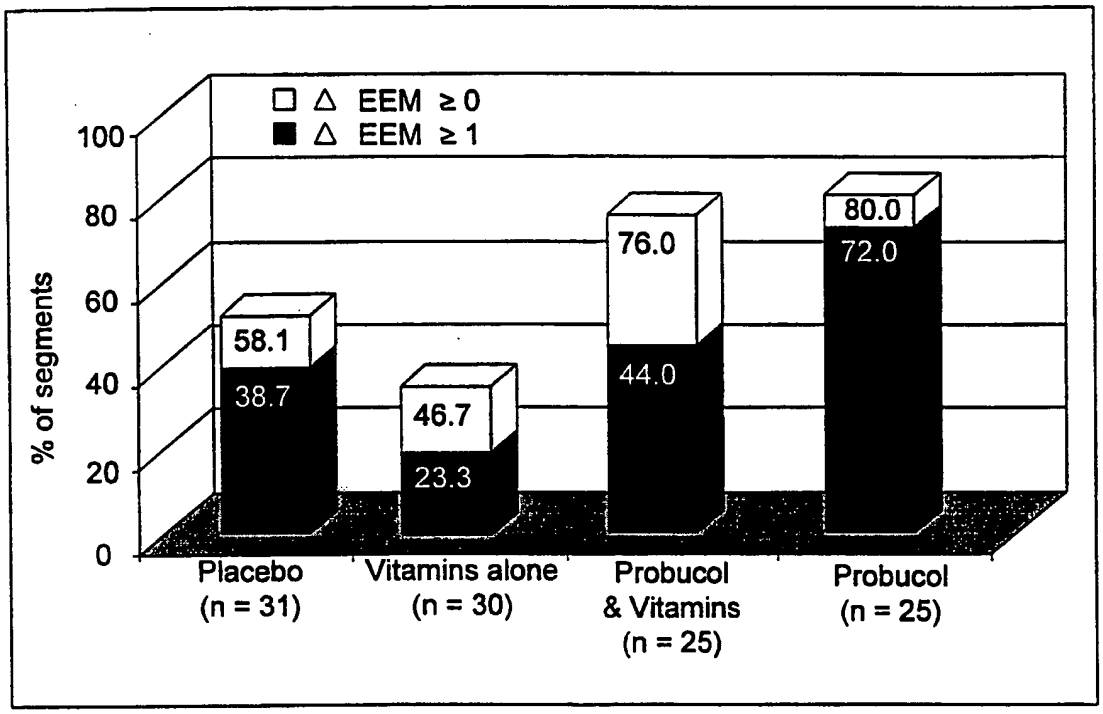
□ △ EEM ≥ 0
■ △ EEM ≥ 1
% of segments
100
80
60
40
20
0
58.1
38.7
46.7
23.3
76.0
44.0
80.0
72.0
Placebo (n = 31)
Vitamins alone (n = 30)
Probucol & Vitamins (n = 25)
Probucol (n = 25)

Fig. 3

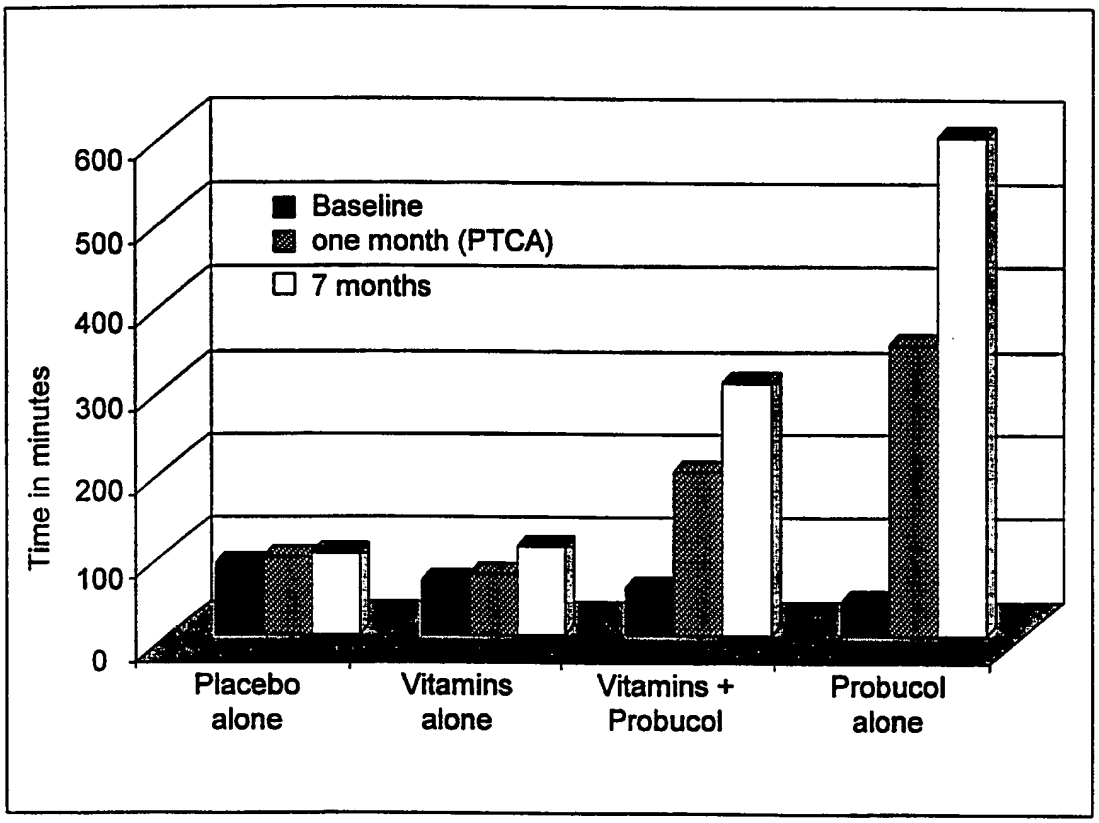
600
500
400
300
200
100
0
Time in minutes
Baseline
one month (PTCA)
7 months
Placebo alone
Vitamins alone
Vitamins + Probucol
Probucol alone

Fig. 4